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γδ T Cell Subsets: A Link Between TCR and Function?

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Abstract

The γδ T lmphocytes are often divided into subsets based upon expression of certain TCR components. This division was initially made because γδ T cells residing in particular epithelia were found to show tissue specific differences in their TCRs. Many examples now show that γδ T cell subsets also appear to be biased to carry out particular functions. This suggests that particular γδ TCR types direct the cells to acquire a certain type of functional programming during thymic development. Here, we describe functionally distinct, TCR-defined γδ T cell subsets, and evidence that their functions are pre-determined in the thymus.

Keywords

γδ T cells; T cell receptor; thymus

Introduction

The γδ and αβ T lymphocytes appear to differ fundamentally from one another in several ways [1]. Both cell types produce many of the same cytokines and bear certain cell surface markers, and can have cytolytic, helper, or regulatory functions. However, whereas the αβ T cells are thymically "educated" to recognize foreign peptides in the context of self MHC, the specificity of the γδ TCRs appears to be focused elsewhere. Moreover, most γδ T cells do not express the coreceptor molecules CD8 and CD4 which are needed for self-recognition via MHC class I and class II. The nature of ligands for the γδ TCR is still not really clear, but substantial evidence now indicates that host derived stress-inducible cell surface glycoproteins are at least in some cases recognized by this type of TCR. In the mouse and human, fewer TCR gene elements (Vs, Ds, and Js) are available to generate γδ TCRs than are available for αβ TCRs, and moreover, many Vδs and Vγs are commonly expressed together, virtually exclusively in some cases, as though there had been a need to further limit (at least in these two species), rather than maximize, the potential diversity of γδ TCRs. Despite this, because it can make D-D joints, the CDR3 region of the TCR-δ chain has more potential for diversity than any other antigen receptor, although this is sometimes abandoned in order to produce TCR-invariant subsets with no diversity at all. It is clear that at least two such subsets in the mouse arise at primarily as the result of developmental mechanisms in the thymus, implying that certain specificities play a vital role and their ample expression must be ensured. We and others have previously noted in a variety of disease models in the mouse that responses of γδ T cell subsets, defined as those that express certain TCR gene

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elements, often correlate with particular functions. This has led us to hypothesize that at least for some γδ T cells, a functional program is imparted to the cells during thymic development, based on the type of TCR that each expresses. Here, we will review examples in which γδ TCR and function were found to correlate, and discuss evidence that supports or refutes this hypothesis.

Vγ1+ functionally distinct γδ T cell subsets

A response by Vγ1+ γδ T cells has in several different systems been noted to correlate with reduced inflammation. First, in mice with myocarditis induced subsequent to infection with coxsackievirus B3, those depleted of Vγ1+ γδ T cells prior to the infection showed an increase in inflammatory infiltrates in the heart muscle and an increase in the percentage of circulating CD4+ cells that produce Th2 cytokines, as compared to sham-treated controls [2]. This indicates that Vγ1+ γδ T cells normally protect against inflammatory damage during coxsackievirus B3 infection. This role is Vγ1-specific, because when Vγ4+ cells were instead depleted, the opposite effect was seen, and the mice developed less severe disease. Consistent with this result, Vγ1+ γδ T cells also have an anti-inflammatory effect in mice infected with *Listeria monocytogenes*, because depleting Vγ1+ cells increased the ability of *Listeria*-infected mice to clear the bacteria, whereas depleting Vγ4+ γδ T cells had no effect in this model [3]. In other work in the *Listeria* model, Vγ1Vδ6.3+ γδ T cells were found to specifically bind to *Listeria*-infected macrophages and lyse them [4], suggesting a mechanism by which Vγ1+ γδ T cells could mediate an anti-inflammatory effect. Many γδ T cells bearing a Vγ1Vδ6.3 TCR have also been shown to have distinct properties akin to those of invariant NKT cells [5,6]. Whether the anti-inflammatory effects of Vγ1+ cells in the myocarditis and *Listeria* models, or the lytic effects of Vγ1Vδ6.3+ cells demonstrated in vitro, are actually mediated by the NKT-like Vγ1+ cells has yet to be determined, however.

The NKT-cell like Vγ1+Vδ6.3+ cells are distinguished by having a nearly invariant TCR, including expression of Dδ2 in only one of three possible reading frames [5]. This subset develops in the thymus of mice during fetal life and the first weeks after birth [7]. These cells resemble the TCR-invariant αβ TCR+ inavariant NKT cells in several additional respects: many express NK1.1, are Thy1-dull, are low for HSA and CD62L, and have high levels of CD44 [8]. The NKT-like γδ T cells appear to be functionally related to the αβTCR + inavariant NKT cells as well [9], and when stimulated produce high levels of both IL-4 and IFNγ, as is typical of NKT cells [8]. Because they appear to recirculate to and reside in the adult thymus [8], this subset can be easily mistaken for newly developed γδ TCR+ thymocytes, but it is also comparatively abundant in the liver [6]. So far, this subset has not been definitively demonstrated to respond specifically in any disease model. The Vγ1Vδ6.3+ cells that respond during *L. monocytogenes* infection seemed likely candidates, but sequencing of Vγ1 and Vδ6 transcripts from the spleens of *L. monocytogenes*-infected mice indicated that their TCRs are much more diverse than those of the NKT-like Vγ1Vδ6.3 subset [10]. A predominant response by γδ T cells that produced high levels of IL-4 was previously noted in mice following *Nippostrongylus brasiliensis* infestion of the gut, which might represent a response of the Vγ1Vδ6.3-invariant subset, because abundant production of IL-4 is quite unusual among γδ T cells [11]. As well, Thy1-dull γδ T cells were found to respond preferentially in the liver of *L. monocytogenes* infected mice [12], and in the peritoneal cavity of some strains of mice when infected with *E. coli* [13], either of which also might represent a response of the invariant Vγ1Vδ6.3+ subset. In any case, mice transgenic for a TCR of this type, when on a Rag1−/− background, all developed spontaneous dermatitis, suggesting an overall proinflammatory role for the Thy1-dull Vγ1Vγ6.3 subset [14]

Vγ1+ cells that instead co-express Vδ5 have been demonstrated to have a enhancing effect on airway hyperresponsiveness (AHR) in mice that have been sensitized to ovalbumin and challenged by airway exposure to the same antigen [15–17]. No prior treatment with sensitizing antigen is needed to induce this function, because Vγ1Vδ5+ γδ T cells from naïve mice can transfer the activity [16], and in fact, AHR-enhancing Vγ1+ cells acquire this ability developmentally before they even exit the thymus [17]. The Vγ1Vδ5+ cells might mediate this function by inhibiting the development of CD4+CD25+ regulatory T cells, since CD4+CD25+ IL-10-producing cells were found to be increased in mice following depletion of Vγ1+ cells [18]. However, this mechanism could be quite complex and involve several cell types, since the AHR-enhancing activity of Vγ1Vδ5+ cells requires that αβ TCR + invariant NKT cells are also present in the responding mouse [16]. In mice unable to produce either IL-4, IFNγ, or TNFRp75, the Vγ1+ cells that develop lack this functional ability, but transfer experiments showed that production of neither IL-4, IFNγ, nor TNFRp75 by the Vγ1+ cells themselves is required for them to exert their enhancing effect [17].

In AHR induced by ozone exposure, Vγ1+ cells appear to play a similar role. In this model, the ability of Vγ1+ cells to promote airway hyperresponsiveness was found to be dependent upon TNFα, since administering anti-TNFα antibody blocked their effect. TNFα production by the Vγ1+ cells themselves was not required, however, since those from TNFα−/− donors were still able to adoptively transfer AHR to TCRδ −/− hosts [19]. It seems likely that these Vγ1+ cells represent a subset identical to the Vγ1Vδ5+ γδ T cells that promote AHR in the ovalbumin model, but those in the ozone model have not been further characterized.

Recently, we also found that Vγ1+ cells promote the development of IgE, induced by immunization with ovalbumin in alum [20]. Like the cells that enhance airway hyperresponsiveness, Vγ1Vδ5+ cells enhanced IgE, but Vγ1Vδ5− cells also showed some enhancing ability, implying that co-expression of one particular Vδ is not a characteristic of this subset. Therefore, the IgE-enhancing function of the Vγ1+ cells is likely an activity that is distinct from that of the airway-enhancing function of Vγ1Vδ5+ cells.

Vγ4+ functionally distinct γδ T cell subsets

In several of the disease models listed above, the functional role of Vγ4+ γδ T cells was also examined and was found to be distinct from that of Vγ1+ γδ T cells, and in three cases, the Vγ4+ cells in fact produced an effect exactly opposite to that of Vγ1+ cells. One such case was noted in coxsackievirus B3-induced myocarditis, in which depletion of Vγ4+ cells protected against the disease rather than exacerbating it as does depleting Vγ1+ cells; the mice showed a reduction rather than an increase in inflammatory infiltrates in the heart, and a larger rather than a reduced percentage of CD4+ Th2 cells in the peripheral blood, compared to sham-treated controls [2]. This indicates that Vγ4+ cells, in contrast to the protective role of Vγ1+ cells, normally promote the heart inflammation induced by infection with this virus.

A second case in which Vγ4+ and Vγ1+ cells appear to play directly opposite roles was seen in the ovalbumin-induced AHR model [15,21]. Here, we noted that adoptive transfer of Vγ4+ γδ T cells into mice incapable of making these γδ T cells resulted in a decrease in AHR induced by ovalbumin sensitization, in contrast to the increase seen when Vγ1+ cells were transferred into TCRδ−/− hosts. Unlike the Vγ1+ cells which require no induction and appear to acquire their AHR enhancing ability even before they exit the thymus, the Vγ4+ cells must first be induced by sensitization and challenge with ovalbumin, before they acquire the ability to suppress AHR [22]. Moreover, their induction requires "preparation" by CD8 dendritic cells (DC), which must be present at the time of antigen sensitization and

must express CD8 [23,24]. Unlike the AHR-enhancing Vγ1Vδ5+ cells, if the Vγ4+ AHR suppressive γδ T cells co-express any particular Vδ(s), we have not been able to demonstrate it. Although they do not require antigen induction, AHR-enhancing Vγ1Vδ5+ cells do require the presence of CD8+ DC during their development [24], so the Vγ1+ AHR-enhancing cells and Vγ4+ AHR-suppressive cells are alike in their dependence on this particular type of DC.

We recently reported a third example in which directly opposite roles were found for Vγ4 vs. Vγ1+ cells, in the ovalbumin-induced IgE model. Paralleling our results in the AHR model, we found that Vγ4+ cells suppress IgE production following adoptive transfer if they are taken from mice first systemically sensitized to ovalbumin, and then tolerized to this antigen by way of airway exposure to aerosolized ovalbumin on ten consecutive days [20]. This finding was in keeping with an earlier report that γδ T cells from mice so treated suppress ovalbumin-specific IgE production [25]. Because the IgE-suppressive Vγ4+ cells in contrast to the Vγ1+ cells in this model require antigen induction, as do the Vγ4+ cells that suppress AHR, we suspected that the Vγ4+ cells in the two different models might in fact represent exactly the same subset. However, this does not seem to be the case, because we have since found that purified Vγ4+Vδ5+ cells show enhanced IgE suppression compared to mixed Vγ4+ cells expressing other Vδs, and that the Vγ4+ cells themselves must also express the CD8 molecule in order to have IgE suppressive activity, neither of which fits with our observations for Vγ4+ AHR suppressive cells [20].

In the *Listeria* infection model, though we found that Vγ1+ cells decrease the ability of the mice to clear the bacteria, Vγ4+ cells did not appear to be playing a role. However, if both Vγ4+ and Vγ1+ cells were depleted before infecting mice with *Listeria*, this abrogated the effect of depleting only the Vγ1+ cells, such that an improvement in bacterial clearance could no longer be detected [3]. This implies that the Vγ1 and Vγ4+ γδ T cells are in some way acting at cross purposes to one another in this disease model as well. The Carding laboratory recently reported that, in contrast to Vγ1+ cells that lyse *Listeria*-infected macrophages, Vγ4+ cells in *Listeria*-infected mice can reduce liver damage inflicted by CD8+ αβ T cells. This function requires that the Vγ4+ cells have the ability to secrete IL-10 [26].

A very tightly-defined Vγ4+ subset was also noted to respond in mice during collagen-induced arthritis (CIA), and were found in the draining lymph nodes of arthritic joints, and in the joints themselves. These cells are nearly all Vγ4Vδ4+ and express a particular amino acid sequence "motif" in both their TCR-γ and -δ junctions, and the majority them produce IL-17. They play a role in exacerbating the arthritis, increasing both the frequency of the disease and its severity [27]. Acquisition of an activated phenotype – CD62L-low, CD45-high, and CD45RB-low – was noted on Vγ4+ cells in the draining lymph nodes during the course of CIA, whereas Vγ1+ cells, which were tracked at the same time, showed little change. An exacerbating role for IL-17-producing γδ T cells in CIA was also confirmed by a later study [28]. In contrast, Vγ1+ γδ T cells do not seem to respond during CIA, and depletion of Vγ1+ γδ T cells in mice in which CIA had been induced had no effect on the subsequent disease incidence or severity [27]. However, an earlier study concerning the role of γδ T cells in CIA suggested that depleting all γδ T cells very late in the disease process instead aggravates the disease [29], rather than improving it as does Vγ4 depletion midway through, so it is possible that another γδ T cell subset plays a different role, at least during the resolution phase of this disease.

The expansion in CIA of a γδ T cell subset with such well-defined TCRs suggests that an antigen is driving the response of γδ T cells having a certain specificity. Although bovine type II collagen, emulsified In Complete Freund's Adjuvant (CFA), is used as an "antigen"

to provoke an autoaggressive attack on the joints in the CIA model, there was no evidence that the responding Vγ4Vδ4+ cells actually recognize collagen. In fact, the same subset responded nearly to the same degree if the mice were treated with CFA only (emulsified with PBS) [27], even though such mice do not develop arthritis. Thus, either CFA itself or a host antigen/signal evoked by the ensuing inflammation would have to be stimulating the response of this subset. Alternatively, a Vγ4Vδ4 subset having these very limited TCR junctions might already pre-exist, and its response could instead be triggered through receptors other than the TCR. TCR-independent stimulation is possible because evidence already exists that Vγ6Vδ1+ T cells [30] and perhaps other γδ T cell subsets as well [31,32] can produce IL-17 when stimulated via receptors other than the TCR, including cytokine receptors and pattern-associated molecular pattern receptors (PAMPs). A subset of γδ T cells with similar properties to the Vγ4Vδ4+ subset that responds during CIA in fact was recently reported, which develops in the thymus of normal mice. Like the CIA-induced subset, these cells are nearly all Vγ4+, plus a high percentage also expresses IL-17, they are present in the skin-draining lymph nodes, and they express low levels of CD45RB. Unlike other γδ T cells, this spontaneously-arising subset also expresses a scavenger-like receptor called Scart2 [33]. Whether the Scart2+ subset and the CIA-induced subset are in fact one and the same is not yet clear; in particular, it remains to be tested whether the CIA-induced Vγ4Vδ4+ cells are also Scart2+, or whether the Scart2+ cells preferentially co-express Vδ4.

Finally, Vγ4+ γδ T cells are also preferentially found among the infiltrating T cells in the brains of mice in the acute phase of experimental autoimmune encephalomyelitis (EAE) [32]. Most of these appear to be functionally alike, because a very high percentage produce IL-17. This characteristic also suggests that they again represent the same Vγ4+ subset that preferentially responds in the draining lymph nodes and joints of mice with CIA. However, whether EAE-induced cells co-express Vδ4, and whether their TCR junctions tend to have the "motif" also identified among those in the CIA-induced subset, was not examined in this study.

Mouse disease models in which TCR-invariant Vγ6Vδ1+ γδ T cells play distinct functional roles

In the mouse, two TCR-invariant γδ T cell subsets develop in the thymus during late fetal and early newborn life. The TCRs they express, which are Vγ5Vδ1+ and Vγ6Vδ1+, despite quite different Vγ regions, are alike in that both express exactly the same δ chain, including an identical amino acid sequence in the junction and the use of Jδ2, which is virtually never found in other mouse γδ TCRs. Vδ1 is found almost exclusively in association with these two Vγs [34]. The invariant sequence of these two TCRs depends upon a lack expression of terminal deoynucleotidyl transferase (TdT), needed for N-region additions, in the thymus at this early timepoint, and the presence of di- and tri- nucleotide repeats near or in the V, D, and J genes involved that act to target the cleavage process during TCR gene rearrangement [35]. The Vγ5Vδ1+ cells home to the epidermis; they are very rare or absent in lymphoid organs or in other epithelial sites [36]. The distribution of the Vγ6Vδ1+ cells is also limited. Originally, they were thought to be confined to the female reproductive tract and oral mucosa [37], but the Augustin laboratory later showed that many resident lung γδ T cell also are Vγ6+ and express the invariant TCR [38,39], and we have recently found that ~15–30% of resident peritoneal γδ T cells are Vγ6Vδ1+ [40].

A predominant γδ T cell response by Vγ6Vδ1+ cells has been shown in a wide variety of disease models. These include *Listeria monocytogenes* infection of the liver [41,42], spleen [42], and peritoneum [40]; *Escherichia coli* infection of the peritoneum [43]; *Listeria*-induced orchitis [44] and autoimmune orchitis [45]; and nephritis, induced in the rat [46] or mouse kidney by adriamycin treatment [47], via Heymann (autoimmune) nephritis in rats

[48], or in intrarenal infection with *L. monocytogenes* [49]. Moreover, in a recently developed model of hypersensitivity pneumonitis (HP) in which a non-pathogenic bacterial strain (*Bacillus subtilis*) is introduced into the airways of mice, an exceedingly strong response by Vγ6Vδ1+ γδ T cells in the lung was noted, such that the infiltrating Vγ6Vδ1+ cells outnumbered both the CD4+ and CD8+ αβ T cells [50]. Strikingly, in all of these disease models, the Vγ6Vδ1+ cells appear to have an anti-inflammatory function. Specifically, depletion of the γδ T cells during the course of the disease exacerbates inflammatory liver damage in *Listeria*-infected mice [51], increases damage to the testis and accelerates the disease in *Listeria*-induced orchitis [52], increases kidney fibrosis and inflammation in the kidneys of mice with adriamycin-induced [47] or *Listeria*-induced nephritis [49], and increases lung inflammation and subsequent fibrosis in *B. subtilis*-induced HP [50]. Consistently, *Listeria*–infected Vδ1−/− mice were shown to develop more large, abscess-like liver lesions, compared to wildtype controls [42]. This suggests that the Vγ6Vδ1+ cells carry out a similar function in all of these disease models.

However, Vγ6Vδ1+ cells have also been reported to play a pro-inflammatory role, and clearly contribute to the host's ability to clear bacteria in models involving either *L. monocytogenes* infection [42], *E. coli* infection [53], or *B. subtilis* treatment [54], and in *E. coli*-infected mice, they have been shown to promote the early infiltration of neutrophils into infected sites [30]. Furthermore, when the cytokines produced by the Vγ6Vδ1+ cells responding in various models are examined, differences become apparent. Such discrepancies in the cytokines produced by Vγ6Vδ1+ cells in various models may stem from the differences in the cytokine millieu in each that act on the Vγ6Vδ1+ cells. Specifically, the infiltrating Vγ6Vδ1+ cells in the kidneys of mice with adriamycin-induced nephritis were shown to express TGFβ, which likely mediates their anti-inflammatory effect; they did not produce IL-4, IL-10, or IFN-γ [47]. Production of TGFβ, but not of IL-10 or IL-4 and only low levels of IFNγ, was similarly reported for the kidney-infiltrating Vγ6Vδ1+ cells in mice with nephritis induced by *L. monocytogenes* intrarenal infection [49]. In contrast, the proinflammatory effects of Vγ6Vδ1+ cells in models involving live bacteria appear to stem from their ability to secrete IL-17 and IFNγ, as was noted in both *L. monocytogenes* infection [40,42,55] and *E. coli* infection [30,43]; secretion of IL-17, but not IFNγ, by the Vγ6Vδ1+ cells was also noted in the *B. subtilis*-induced HP model [54]. Despite this, the Vγ6Vδ1+ cells in the models involving live bacteria were nonetheless responsible for an overall anti-inflammatory effect. This may stem from co-production of cytokines with anti-inflammatory properties, in addition to the pro-inflammatory IL-17 and IFNγ; these cytokines do not appear to be TGFβ, IL-4, or IL-10. In the case of *B. subtilis*-induced HP, the responding Vγ6Vδ1+ cells in the lungs of these mice were found to co-produce IL-22 [54], which is a potential candidate. Although this "Th17"-associated cytokine has anti-bacterial effects, it has also been shown to protect against inflammatory damage in the liver and intestinal epithelium [56,57]. Thus, although in all cases the Vγ6Vδ1+ cells act to reduce inflammatory damage overall, they may be fairly malleable in terms of the cytokines they are induced to secrete which give this result. The degree to which they differ is not yet clear, however, and whether they are also producing IL-17 in addition to other cytokines in the models described above that do not involve live bacteria has yet to be determined.

Evidence for TCR/function correlations among human γδ T cells

The two major γδ T cell subsets that have been studied in the human immune system are the Vγ9Vδ2+ cells that predominate among γδ T cells in the circulation, and the Vδ1+ γδ T cells (co-expressing a variety of Vγs that are often members of the VγI family, rather than Vγ9 which is a member of the VγII family [1]). The Vδ1+ cells comprise a minor population in the blood but are common in the intestinal epithelium and spleen [58]. In a study in which peripheral blood-derived Vδ2 and Vδ1+ cells were first expanded in vitro, and then

stimulated with LPS, many differences between the two were seen with regard to the transcripts that were induced [59]. In agreement with previous studies that showed production of pro-inflammatory cytokines including IFNγ and TNFα by Vγ9Vδ2+ cells following in vivo and in vitro stimulation [e.g. see [60,61]], the Vδ2+ cells showed greater elevation in transcripts encoding proinflammatory cytokines, including IL-17 as well as IFNγ and TNFα, whereas the Vδ1+ cells showed a greater increase in IL-10 transcripts; both subsets showed strong induction of genes involved in NK cell-like killing [59]. Thus, certain inherent functional differences are apparent between human TCR-defined γδ T cell subsets as well.

Evidence for the functional programming of γδ T cells during thymic development

In a study examining naïve peripheral γδ T cells from various locations in mice, most γδ T cells when stimulated through the TCR were found to express either IFNγ or IL-17, but not both. Although some co-production of TNFα was evident among both the IFNγ and IL-17 producers, neither group co-expressed either IL-4 or IL-10 [62]. At least some γδ T cells appear to acquire these functional biases during thymic development, as a result of turning on the Th17 cytokine-inducing transcription factors RORγT and Runx1 in the case of the IL-17 producers, or the Th1 cytokine-inducing transcription factor Tbet in the case of the IFNγ producers [63]. For the TCR invariant Vγ1Vδ6.3+ subset, expression of the PLZF transcription factor in the thymus is required for functional development, as it is for αβTCR + iNKT cells, and PLZF confers upon both of these T cell types their ability to make rapid cytokines responses and to produce Th1- and Th2-type cytokines simultaneously [14]. The γδ TCR clearly is responsible for the functional imprinting in this subset, because in mice expressing a transgene encoding an invariant-type Vγ1Vδ6.3 TCR, most of the developing γδ TCR+ thymocytes were found to have turned on PLZF expression, which is normally only rarely expressed. Moreover, addition of an antibody specific for the γδ TCR was sufficient to turn on PLZF expression in developing γδ TCR+ thymocytes [14], implying a direct role for the TCR in directing the imprinting of a certain function. However, γδ T cells other than the Thy1-dull Vγ1Vδ6.3+ subset also encounter TCR ligands in the thymus, but it appears that only the Vγ1Vδ6.3+ subset as a result expresses PLZF and acquires the ability to dually produce IL-4 and IFNγ. Therefore, there must be additional factors that normally play a role in the imprinting of this subset.

There is considerable evidence that the skin-homing TCR-invariant Vγ5Vδ1+ cells while developing in the thymus require interaction with a TCR ligand as a positive selection step for their production [64–66]. As dendritic epidermal T cells in the periphery, the Vγ5Vδ1+ subset expresses a rather unusual array of cytokines/chemokines that contribute to their ability to promote wound repair in the skin, including keratinocyte growth factor [67], CCR10 (a receptor for the skin chemokine CCL27) [68], insulin-like growth factor-1 [69], and lymphotactin [70]; unlike most other γδ T cells, they do not produce either IL-17 or IFNγ [62]. Whether a bias to produce this particular array of factors is imprinted onto them during thymic development has not yet been examined, but it has been reported that developing Vγ5Vδ1+ cells from the fetal thymus do not express IL-17 when stimulated with PMA/ionomycin, whereas Vγ6Vδ1+ fetal thymocytes that arise immediately subsequent to them are strong IL-17 producers [62]. Another subset that appears to undergo functional imprinting in the thymus consists of γδ T cells whose TCR-δ chain junctional amino acid sequence includes a particular motif [W(S)EGYEL] which enables them recognize the nonclassical MHC class I molecule, T22 [71]). In strains that express it, these cells appear to encounter T22 as a TCR ligand during thymic development. A recent study showed that if these T22-recognizing γδ TCR+ thymocytes develop in a mouse that can express T22, they become biased to secrete IFNγ, whereas if T22 is not present, they instead become biased to

secrete IL-17 [72]. The authors hypothesized that for γδ T cells in general, those which during thymic development encounter a ligand for their TCR become biased to produce IFNγ, whereas those that fail to encounter a TCR ligand instead become biased to produce IL-17. They also proposed that γδ T cells unlike αβ T cells generally do not require a TCR signal in order to develop into mature cells, because γδ TCRs possess the ability to self-dimerize, thus obviating the need for a ligand to cross-link the TCR. The Vγ5Vδ1 TCR appears to be an exception here because it cannot self-dimerize, and consistently, this subset does not appear to be able to develop without the thymic expression of a specific ligand [66]. Whether the T22-recognizIng γδ T cells in this study actually developed in the absence of thymic ligands was not clear, however; since T22-recognition requires only a particular δ chain junctional motif, γδ TCRs meeting this criterion could potentially also recognize other ligands.

In another study, evidence was presented that the functional imprinting of γδ T cells in the thymus depends upon whether or not γδ thymocytes express CD27; those expressing CD27 secreted IFNγ, whereas those that were negative for CD27 secreted IL-17. The authors proposed that CD27 in fact regulates IFNγ vs. IL-17 differentiation, since γδ T cells from mice with a genetically ablated CD27 gene were deficient in IFNγ production whereas their IL-17 production was unaffected, and that it accomplishes this by inducing expressing of the LTβ receptor [63]. What controls the expression of CD27 during the thymic development of γδ T cells was not determined in this study, however. In agreement with the T22 study [72], generation of IFNγ-producing γδ TCR+ thymocytes here was also found to also require in addition to CD27 a signal through the TCR itself. Thus, together these studies [14,62,63,72] indicate that the γδ TCR itself dictates the type of function that developing γδ T cells acquire during thymic maturation in at least some cases.

The CD27 study also presented evidence that during infection, γδ T cells largely maintain their functional bias, such that CD27+ γδ T cells isolated from mice infected with *Plasmodium berghei* continue to be biased to produce IFNγ, whereas CD27- γδ T cells remain biased to produce IL-17 [63]. This finding is in agreement with in vitro studies carried out earlier, in which it was found that although culturing splenic γδ T cells under Th2-polarizing conditions did induce more of them to produce IL-4, the fraction that was biased to produce IFNγ remained unchanged [73]. Moreover, IL-4 producing γδ T cells from Th2-polarizing cultures continued to express the IL-12Rβ chain, even though no IFNγ was present in the system and the cells turned on expression of the Th2-cytokine inducing transcription factor GATA-3. Further investigation revealed that Tbet expression in γδ T cells stimulated through their TCR is not down regulated by culture in the presence of IL-4, as has been reported for CD4+ αβ T cells [74], implying that αβTCR+ CD4+ T cells and γδ T cells regulate transcription factors differently. These findings indicate that many if not all γδ T cells are less "plastic" than αβ T cells, and that once they have been functionally programmed in the thymus, they typically preserve that function when activated peripherally.

Conclusions

Whether all TCR-defined γδ T cell subsets have predetermined functions that are programmed into them during thymic development, or whether the function can instead be induced in a given subset when it is triggered to respond in the periphery, is not always clear. In many cases, the "function" may be defined only in terms of producing particular symptoms, and has not yet been correlated with any molecular mechanism. However, at least for the three TCR-invariant γδ T cell subsets in mice – the Vγ5Vγ6 epidermal subset, the Vγ6Vδ1 subset elicited in inflammation elicited in many different ways, and the Thy1-dull Vγ1Vδ6.3+ cells that reside in the adult thymus – a functional program does indeed

appear to be thymically imprinted at least in part, because cytokine biases attributed to each of these subsets during peripheral responses can also be detected when the cells are still developing in the thymus.

Because functionally distinct γδ T cell subsets can be defined by their TCRs, such findings may imply that the function of the γδ TCR may be restricted to directing functional imprinting in the thymus, rather than in eliciting peripheral responses. For the TCR-invariant Vγ5Vδ1+ cells that colonize the murine epidermis, the TCR appears to be required for both, because this subset fails to develop in the thymus in the absence of a specific TCR ligand [66], whereas Vγ5Vδ1+ cells in wounded skin show evidence of TCR stimulation in that in those near the wound site, the TCR becomes polarized in lipid rafts oriented towards the wound [75]. However, at least in some cases, the γδ TCR does not appear to be necessary to trigger a response in the periphery. For IL-17-producing γδ T cells, it was shown that secretion of this cytokine can be triggered in Vγ6Vδ1+ cells by IL-23 alone [30], or in peritoneal γδ T cells by IL-23 plus a ligand for a PAMP receptor [31]; additionally, strong IL-17 production was induced in Vγ4Vδ4+ cells with a combination of IL-1, IL-7, and IL-23 in the absence of any deliberate TCR triggering [76].

One puzzling question is why in many cases responses by distinct γδ T cell subsets in the same disease model have been noted whose functions appear to be exactly opposed to one another. Their responses would then appear to cancel one another out, and be of no utility. However, in such cases, it is sometimes clear that the effect of one γδ T cell subset is dominant over that of another, such that the consequence of the first subset may be dampened but is not erased by the response of the second. For example, among γδ T cells that affect the IgE response to ovalbumin, where Vγ1+ γδ T cells promote but Vγ4+ γδ T cells can be induced that suppress IgE, the net effect of reconstitution using a full complement of γδ T cells from an ovalbumin-induced mouse was IgE suppression, although the effect was somewhat weaker than if Vγ4 cells only were transferred. This showed that the Vγ4+ cells, when induced in this model, are dominant over the Vγ1+ cells [20]. Such functionally opposed subsets may allow γδ T cells to act as regulatory cells that balance the overall immune response, allowing neither a pro-inflammatory nor an anti-inflammatory state to become too pronounced.

Abbreviations

AHR	Airway hyperreactivity
DC	Dendritic cells
PAMPs	Pattern-associated molecular pattern

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